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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/039,171
Filing Date: January 03, 2002
Appellant(s): HALEY ET AL.

Steven Highlander
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/22/09 appealing from the Office action mailed 10/2/08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6521226 Radtke

5721118 Scheffler

Li et al. Toxicology Letters 76:219-226, 1995

Humbert et al. 3:73-76, 1993

Davies et al. Nat. Genet 14:334-336, 1996

Adkins Am. J. Hum. Genet 52:598-608, 1993

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 10-13, 17-25, 37-39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radtke (US 6,521,226) taken with Li et al. (C39) and Davies et al. (C14), Adkins (C2), and Humbert et al. (C26). Radtke teaches that paraoxonase-1 (PON-1), when expressed has hydrolase activity for organophosphate. See columns 1 and 15-16. Furthermore, Radtke teaches, "...PON is a protein secreted by the liver that is found primarily in the liver" and "The name is derived from its ability to hydrolyze the organophosphate paraoxon in vivo" (column 2, lines 30-32) and "It is well known to be involved in the hydrolysis of several organophosphate insecticides" (column 2, lines 37-39). Radtke teaches that PON1 type R and Q are known variants in humans (columns 4-5 and 15-16). Radtke teaches using PON 1 in gene therapy using a number of viral vectors comprising and methods of successful delivery and expression are known in the prior art (column 8-9). PON1 type Q phenotype has been correlated with higher paraoxonase activity than the type R phenotype (column 8). Radtke teaches using several routes of administration (including intravenous) to deliver the composition to a subject (column 6). An assay can be used to measure either phenotype or the ratio of the two phenotypes present in an individual (column 8). However, Radtke does not specifically teach identifying a subject at risk or exposed to an organophosphate toxin

and administering an expression cassette comprising a nucleic acid encoding PON1 to the subject.

However, at the time the invention was made, Li et al. teach that paraoxonase protects animals against an organophosphate toxin (page 219). Li further teaches identifying animals that have been exposed to an organophosphate toxin (pages 220-221). Li teaches intravenous (i.v.) administration of PON to a mouse exposed to an organophosphate toxin (page 221).

In addition, at the time the invention was made, for three decades it has been established that the main determinant of susceptibility to organophosphate poisoning is the activity level of PON 1 isoenzymes, and this relationship has been shown to hold across many species including humans. Davies teaches, "interspecies differences in PON1 activity correlate well with observed median lethal dose (LD_{50}) values [of organophophates]." See abstract. Adkins and Humbert teach that PON1 type R hydrolyzes paraoxon rapidly (page 598 and page 73, respectively). Davies teaches that PON1 type Q efficiently hydrolyzes diazoxon, soman and sarin (page 334).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to identify a cell or subject exposed to an organophosphate toxin and express PON 1 in a cell or subject exposed to the organophosphate toxin. One of ordinary skill in the art would have been motivated to combine the teaching to protect a cell or subject from an organophosphate toxin since PON1 is known to hydrolyze an organophosphate toxin. "The combination of familiar

elements according to known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to intravenously administer a nucleic acid encoding PON1 type R or PON1 type Q to a subject exposed to paraoxon. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently deliver the nucleic acid to cells for expressing PON1 type R and PON1 type Q is known to rapidly hydrolyze paraoxon and PON1 type R hydrolyzes organophosphate compound.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to intravenously administer a nucleic acid encoding PON1 to a subject or cells express low levels of PON1 type Q or R as compared to general population. One of ordinary skill in the art would have been motivated to combine the teaching to increase expression of PON 1 type Q or R or since PON type Q is known to rapidly hydrolyze an organophosphate compound.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to administer a viral vector (e.g., adenoviral vectors, adeno-associated viral vectors or retroviral vectors) comprising nucleic acid

encoding PON1 to a subject exposed to an organophosphate toxin. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently deliver the nucleic acid to cells.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to liver cells a nucleic acid encoding PON1 to a subject or cell exposed to an organophosphate toxin. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently deliver the nucleic acid to cells and PON is secreted by the liver.

In addition, the method in claims 17 and 18 are obvious because the method taught by Radtke, Li, Adkins, Humbert, and Davies uses the same material and method steps as recited in claims 17 and 18. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 9, 14-16, 21, 36, and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radtke taken with Li, Davies, Adkins, and Humbert as applied

to claims 1-5, 10-13, 17-25, 37-39 and 43 above, and further in view of Scheffler (US 5,721,118).

However, Radtke taken with Li, Adkins, Humbert, and Davies taken with do not specifically teach using a polyadenylation (poly A) tail in the vector.

However, at the time the invention was made, one of ordinary skill in the art understands that poly A tail protects mRNA molecule from exonucleases and is important for transcription termination, for export of the mRNA from the nucleus and for translation. Scheffler teaches using poly A tail for regulating gene expression (column 5). In addition, tissue-specific, constitutive, and inducible promoters for expressing a gene of interest were well known to one of ordinary skill in the art as exemplified by Scheffler (column 6).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke, Li, Adkins, Humbert, and Davies taken with Scheffler, namely to make and use a poly A tail in the vector in the method. One of ordinary skill in the art would have been motivated to combine the teaching for protecting the mRNA from exonucleases and for proper polyadenylation of the gene transcript.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke, Li, Humbert, Adkins, and Davies taken with Scheffler, namely to make and use a promoter selected from a constitutive promoter, an inducible promoter, or a tissue specific promoter in the vector in the method. One of ordinary skill in the art would have been motivated to

combine the teaching for properly or efficiently expressing the DNA encoding PON1 in a desired cell.

In view of the teaching of Radtke, Li, Humbert, Adkins, Davies, and Scheffler, one of ordinary skill in the art would have had a reasonable expectation of success for practicing the method because the promoter were well known to one of ordinary skill in the art for expressing a heterologous nucleic acid in a cell.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

(10) Response to Argument

i.) Radtke, Li, Adkins, Humbert and Davies

In response to appellant's argument that Li et al. provides no motivation to use PON1 Q and R for treating or preventing OP toxicity because Li et al. isolated PON from rabbits not PON1 and it is not certain what types of PON were known for protecting animals from chlorphyrifos toxicity, the appellant's argument is not found persuasive because if Li taught the claimed invention by itself a 102 rejection would have been made instead of a 103 rejection. In addition, only some of the claims are limited to either using PON1 type Q or PON1 type R in the claimed method. Furthermore, the totality of the prior art of record teaches that one of ordinary skill in the art that PON1, including PON1 type R and PON 1 type Q can be used to hydrolyze organophosphate. Furthermore, Radtke teaches, "...PON is a protein secreted by the liver that is found primarily in the liver" and "The name is derived from its ability to hydrolyze the

organophosphate paraoxon in vivo" (column 2, lines 30-32) and "It is well known to be involved in the hydrolysis of several organophosphate insecticides" (column 2, lines 37-39)

In response to appellant's argument that Davies' demonstration of substrate specificity for PON1 Q and R on serum samples tested in vitro was not sufficient to demonstrate that boosting PON1 Q and R isoezymes concentrations in vivo would successfully protect OP poisoning, the appellant's argument is not found persuasive because if Davies taught the claimed invention by itself Davies would have been cited under 102 and not 103. The totality of the prior art of record teaches that one of ordinary skill in the art that PON1, including PON1 type R and PON 1 type Q can be used to hydrolyze organophosphate.

Appellant's assertion that even though Davies teaches a role of PON1 type Q and type R in protection from OP toxicity and differential potency of the PON 1 type Q and R isoenzymes hyrdrolyzing different OPs, one of ordinary skill in the art could not reasonably correlate from an in vitro working example to practicing the claimed method is not supported by any evidence of record. "The arguments of counsel cannot take the place of evidence in the record." See In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

In response to appellant's argument that the entirety of the cited references fail to indicate what will happen when one boosts the levels of PON1 (or PON1 Q), the appellant's argument are not found persuasive because the prior art of record teaches that PON protects animals against an organophosphate toxin (see Li, page 219) and

PON-1 when expressed has hydrolase activity for organophosphate (Radtke, column 1, lines 15-16).

In response to appellant's argument that they were the first to demonstrate that substrate specificity was successfully produced by boosting PON1 Q and R levels in vivo removing the uncertainty over the many possible pertubing influences and demonstrating that no apparent toxic effects limited its usefulness, the argument is not found persuasive because at the time the invention was made, PON 1 enzymes, including PON 1 type Q and PON 1 type R were known to one ordinary skill in the art for hydrolyzing organophosphate toxins. See Adkins, Humbert, Davies, and Radtke. In addition, expression of a protein in cells in vivo using nucleic acid delivery was well known to one of ordinary skill in the art. In addition, several of the claims are not limited to expressing PON1Q or R. The claims that are limited to PON1 Q and R are obvious in view of the totality of the prior art of record.

Appellant's assert that, 'Without this information, one skilled in the art could not possible have assured that a genetic therapy for OP toxicity could be successfully produced and offered.' WIth respect to appellant's assertion, there is no evidence of record to support the assertion. "The arguments of counsel cannot take the place of evidence in the record." See In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

In response to appellant's argument that the examiner has attempted to counter these strong arguments not by any scientific rebuttal, but by taking refuge behind three legal princicples and all of the argument are false, the argument is not found persuasive

because the examiner is following the guidelines for a 103 rejection as set forth in MPEP 2141-2145. The examiner ascertained the differences between the claimed invention and the prior art: The differences between the claimed invention and prior art were using a nucleic acid encoding PON1 to protect or treat a cell exposed to an organophosphate toxin whereas the prior art taught that expressing PON1 could treat or protect cells from an organophosphate and delivering a nucleic acid to a cell in vivo was well known one of ordinary skill in the art (see Radtke). Resolving the level of ordinary skill in the pertinent art: One of ordinary skill in the art could reasonably expect to express a desired protein encoded by a nucleic acid in vivo (see Radtke).

> "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton."KSR, 550 U.S. at ___, 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle."Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ."Id. at ___, 82 USPQ2d at 1396. In addition to the factors above, Office personnel may rely on their own technical expertise to describe the knowledge and skills of a person of ordinary skill in the art. The Federal Circuit has stated that examiners and administrative patent judges on the Board are "persons of scientific competence in the fields in which they work" and that their findings are "informed by their scientific knowledge, as to the meaning of prior art references to persons of ordinary skill in the art." In re Berg , 320 F.3d 1310, 1315, 65 USPQ2d 2003, 2007 (Fed. Cir. 2003). See MPEP 2141 II 2(c).

In addition, at the time the invention was made, there was a reasonable expectation of success of using nucleic acid delivery to efficiently express a protein of interest in cells in vivo (See Radke, of record). "The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success." See Agrizap, Inc. v. Woodstream Corp., 520 F.3d 1337 (Fed. Cir., 2008) and In re Merck & Co., Inc., 800 F.2d 1091,231 USPQ 375 (Fed. Cir. 1986). Also see Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007), "when there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." "If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."

In response to appellant's argument that they believe that USPTO is estopped in this case from taking the position that gene therapy is predictable since prior office actions dated August 23, 2005 and May 17, 2006 contain enablement rejections against the claimed invention, the appellant's argument is not found persuasive because as set forth in previous office actions, applicant's argument successfully rebutted the prima facie enablement rejection. Thus, the enablement rejection was withdrawn based on applicant's arguments. "To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing." "The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or

sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled." See MPEP 2164.05.

In response to appellant's argument that the appellant is not arguing against the reference individually but pointing out specific facts from each reference that undercut the examiner's attempted extrapolations, the argument is not found persuasive because the totality of the prior art teaches that one of ordinary skill in the art would have had motivation to combine the references to arrive at the claimed invention. "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments." See Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

In response to appellant's argument that there is clearly no "finite number of identified predictable solutions" from which the skilled artisan could choose and the failure of Radtke to exploit this allegedly "obvious" aspect of PON1 gene therapy, the argument is not found persuasive because at the time the invention was made, PON 1 enzymes, including PON 1 type Q and PON 1 type R were known to one ordinary skill in the art for hydrolyzing organophosphate toxins. See Adkins, Humbert, Davies, and Radtke. In addition, expression a protein in cells in vivo using nucleic acid delivery was well known to one of ordinary skill in the art. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See *KSR v. Teleflex,* 550 U.S. , 127 S. Ct. 1727 (2007). Furthermore, even though Radtke teaches, "...PON is a protein secreted by the liver

that is found primarily in the liver" and "The name is derived from its ability to hydrolyze the organophosphate paraoxon in vivo" (column 2, lines 30-32) and "It is well known to be involved in the hydrolysis of several organophosphate insecticides" (column 2, lines 37-39), neither the office nor the applicant was in position to know why Radtke did not specifically describe the claimed invention.

ii.) Radtke, Li, Adkins, Humbert, Davies, and Scheffler

Appellant's arguments against this rejection have already been addressed in the response to the argument's against Radtke, Li, Adkins, Humbert and Davies. Appellant has not set forth additional arguments against this 103 rejection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Brian Whiteman/
Primary Examiner, Art Unit 1635

Conferees:

/JD Schultz/

Supervisory Patent Examiner, Art Unit 1635

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